

### **REMARKS**

In the Office Action mailed January 21, 2009, claims 1-30 and 35-37 were pending for consideration. All of the claims were rejected on various statutory grounds, each of which is addressed in turn below. The Applicant respectfully submits that the present claims are allowable over the cited references.

#### **Claim Rejections – 35 U.S.C. 112**

The Examiner has rejected claims 1-22, 24-30, and 35-37 under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Examiner has argued that it is unclear how the use of an auxiliary chamber can enhance the concentration of the sample in the isoelectric focusing device. The description of the auxiliary chamber and how concentration is enhanced is found in, *inter alia*, paragraphs [0008] and [0035] of the specification as filed.

As is described in paragraph [0008], the sample holding volume is increased by adding at least one auxiliary compartment to the separation capillary. The Examiner has argued that such an increase in volume would reduce the concentration of the ampholyte because the ampholyte can now take up the entire space 42 shown in FIG. 3, and that this “is not in any reasonable sense and increase in ampholyte concentration.” The Examiner is confusing the system at rest with the system during isoelectric focusing. Because the auxiliary chambers increase the volume of the system, more volume can be processed in the separation capillary. When current is applied between the anode and the cathode, a greater concentration of carrier ampholyte is thus utilized to increase the focusing of the system, or in other words increase the concentration of the ampholyte being separated in the separation capillary. When auxiliary agents are used, they migrate to the

corresponding anode or cathode thus providing an additional driving force to further concentrate the ampholyte. The important point to note is that the ampholyte is being concentrated during focusing, not at rest, and that the ampholyte is located within the separation capillary at that point, not the auxiliary chambers. Reconsideration is respectfully requested.

Regarding the  $(V_{\text{auxanode}} + V_{\text{sep}} + V_{\text{auxcathode}})/V_{\text{sep}}$  equation, this is merely a function showing the relationship between enhancement and volume. As the total volume of  $(V_{\text{auxanode}} + V_{\text{sep}} + V_{\text{auxcathode}})$  increases, the enhancement of the focusing is increased as compared to  $V_{\text{sep}}$ .

#### **Claim Rejections – 35 U.S. C. 103 – Vigh and Valmet**

The Examiner has rejected claims 1, 3-4, 7-30, and 35-37 under 35 U.S.C. 103(q) as being allegedly unpatentable over U.S. Patent App. No. 2002/0043456 (hereinafter “Vigh”) in view of U.S. Patent No. 3,616,456 (hereinafter “Valmet”).

The independent claims of the present application teach an isoelectric focusing method and apparatus for the separation of analytes without the use of a membrane. An electrical potential established between the present anode and cathode causes the establishment of a pH gradient within the separation chamber (paragraph [0032]). Analytes within the separation device are thus focused at points along the separation chamber based on the isoelectric potential of the analytes in the sample. The auxiliary agent(s) added to the device, either in the separation chamber or in auxiliary chambers, increases the concentration of the amphoteric sample components in the separation chamber, and thus improves the concentration detection limit of the isoelectric focusing system (paragraph [0008]).

Vigh teaches an electronic separation apparatus that utilizes isoelectric membranes to separate components from a sample fluid (paragraphs [0013], [0014], [0015], [0024], [0026], [0037]). As is further described in paragraph [0037], an electric potential is applied to the apparatus to cause the migration of at least one selected component through at least one of the ion-permeable barriers. As such, Vigh is teaching the separation of analytes across an ion-permeable membrane.

Valmet teaches a system for the separation of analytes having an anode, a cathode, and a series of chambers having transverse walls. The fraction in each compartment is precluded from spreading by the shape of the chamber along with the force of gravity. (See col. 3, lines 7-37). While Valmet teaches that comparatively large liquid volumes can be processed by the apparatus, Valmet does not teach or suggest increasing the volume of an auxiliary chamber as compared to the size of the focusing apparatus. As is taught by Valmet, a large volume of liquid can be processed because the wall heights of the individual chambers are increased to accommodate an additional volume of liquid, as is described in col. 6. The present claims do not contain limitations that the separation capillary be increased in volume, but that auxiliary chambers be added to the system to increase the carrier ampholyte that is being processed by the separation capillary. In this case, by adding such auxiliary chambers, the volume of the focusing chamber remains the same while the liquid volume used in the focusing process is increased. As has been explained herein, this added carrier ampholyte functions to more effectively focus the ampholyte in the separation capillary.

Additionally, a combination of Vigh and Valmet would result in a non-functional apparatus. Turning to FIG. 1 of Vigh, the device comprises an electrolyte chamber 22 having an electrolyte inlet 4 and outlet 12, a sample chamber 26 having a sample inlet 8 and outlet 16, and a

semipermeable membrane 30 located between the sample chamber and the electrolyte chamber. As can be seen from the figure, electrolyte is added from the left at input 4 and removed from the right through output 12, while the sample is added from the right through input 8 and removed from the left through output 16. By removing the membrane 30 from this “counter-current” type system, as is suggested by the Examiner, the electrolytes and the sample will liberally mix within the single chamber that is the combination of 22 and 26. Because of the counter-current operation of this device, mixtures of electrolyte and sample would be removed from both the sample outlet and the electrolyte outlet, and separation could not occur. As can be seen in FIG. 2, a power supply applies current along the electrolytes in chamber 22. Without the membrane, the power supply would deliver current to a mixture of electrolyte and sample that is moving out of outlet ports at each end of the apparatus, and thus no separation would occur.

The Applicant thus asserts that the combination of Vigh and Valmet does not teach each and every element of the independent claims of the present application, and that such a combination would result in a nonfunctional device. Reconsideration is respectfully requested. Additionally, those claims that depend from the independent claims are narrower in scope, and it is also requested that these rejections be withdrawn as well.

#### **Claim Rejections – 35 U.S. C. 103 – Speicher and Valmet**

The Examiner has rejected claims 1, 7-24, 27, 29-30, and 37 under 35 U.S.C. 103(a) as being allegedly unpatentable over U.S. Patent No. 6,638,408 (hereinafter “Speicher”) in view of Valmet. Speicher teaches a method and device for the separation of mixtures of charged molecules (col. 2, lines 50-52). Speicher further teaches an apparatus having a chamber for holding a liquid, and a series of membranes for separating analytes into a plurality of

compartments (col. 2, lines 55-64; col. 4, line 57 to col. 5, line 6). As is described at col. 5, lines 55-59, the chamber is divided into separation compartments by porously charged membrane partitions. As is further described by Speicher, upon application of an electrical potential across the series of chambers, charged molecules migrate until entering a chamber where the molecule has a net charge of zero (col. 7, lines 40-46). Thus the molecules are separated by an electric field across charged porous membranes into individual compartments.

The Applicant asserts that the combination of Speicher and Valmut does not teach or suggest each and every element of the present independent claims. Specifically, as is described above, the combination of references does not teach or suggest the use of an auxiliary chamber or auxiliary agents to more effectively focus the ampholyte within a separation chamber.

Additionally, it is reiterated that Speicher does not teach the isoelectric focusing of an analyte. While the term "isoelectric focusing" is used by Speicher in col. 4, lines 50-54 to describe that separation technique, the proper descriptive terminology should be "isoelectric trapping." Isoelectric trapping describes numerous techniques for utilizing an isoelectric potential to trap an analyte on one side of a membrane. Such is the case with Speicher, where analytes are migrated along an isoelectric gradient to be trapped in a chamber surrounded by charged membranes. By removing the trapping membranes, the individual trapping chambers are destroyed, and a single chamber would be the result. Based on the teachings of Valmet, multiple chambers are required to separate the sample, and thus one of ordinary skill in the art would not have sufficient likelihood of success in making such a modification if that modification eliminated the chambers. Reconsideration is respectfully requested. Additionally, those claims that depend from the independent claims are narrower in scope, and it is also requested that these rejections be withdrawn as well.

### **Claim Rejections – 35 U.S. C. 103 - Shave**

The Examiner has rejected claims 1, 3, 4, 7-15, 17-30, and 35-37 under 35 U.S.C. 103(a) as being unpatentable over Electrophoresis Vol. 25, 2004, pp. 381-387 (hereinafter “Shave”). Shave teaches an isoelectric trapping system, which is described by the authors as a system whereby a target protein is trapped in an isoelectric state between two isoelectric membranes (col. 1, p. 381; col. 1, p. 382). Additionally, the Shave system is a continuous flow isoelectric trapping system. As is taught on page 382, first column, last paragraph, the anodic and cathodic agents are added to the respective anodic and cathodic streams and subsequently trapped by respective isoelectric membranes. These agents are trapped within compartments that they flow by in the continuous stream. The presence of the agents in the compartments allows proteins to be trapped and kept in their nonisoelectric charged states. Thus the mechanism of trapping in such a continuous flow system requires membranes to trap the charged moieties out of the stream.

The Applicant asserts that the Shave and Valmet references are not combinable because they such a combination would be non-functional. If the membranes across which the trapping occurs were removed according to Valmet, as is suggested by the Examiner, the result would be a continuous flow of anode and cathode agents and protein with no mechanism for the trapping to occur. Thus, one of ordinary skill in the art would not have sufficient likelihood of success in making such a modification. Reconsideration is respectfully requested, along with those claims that depend from the independent claims.

### **Claim Rejections – 35 U.S. C. 103 – Vigh, Valmet and Hofmann**

The Examiner has rejected the following claims under 35 U.S.C. 103(a) as being allegedly unpatentable:

claims 5 and 6 over Vigh in view of Valmet and Hofmann

claims 3-4, 25, 26, and 28 over Speicher in view of Valmet and Pawliszyn;

claims 5 and 6 over Speicher in view of Valmet, Pawliszyn, and Hofmann;

claims 5 and 6 over Shave in view of Valmet and Hofmann; and

claim 16 over Shave in view of Valmet and Wu.

As has been discussed in the previous sections, Vigh, Valmet, Speicher, and Shave, the primary references in all of the 103 rejections, do not teach each and every element of the independent claims, and/or result in inoperable combinations. As the claim rejections immediately above pertain to dependent claims, they will not be discussed in detail, and it is assumed that they are allowable along with the independent claims from which they depend.

### **CONCLUSION**

In view of the foregoing, the Applicant asserts that claims 1-30 and 35-37 of the present application present allowable subject matter and the allowance thereof is requested. If any impediment to the allowance of these claims remains after consideration of the present amendment and above remarks, and such impediment could be removed during a telephone interview, the Examiner is invited to telephone Todd Alder, or in his absence, Robert Mallinckrodt, so that such issues may be resolved as expeditiously as possible.

Please charge any additional fees except for Issue Fee or credit any overpayment to Deposit Account No. 20-0100.

Dated this 21<sup>st</sup> day of May, 2009.

Respectfully submitted,

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